

ORIGINAL ARTICLE

Anaphylaxis

The health and economic outcomes of early egg introduction strategies

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Abstract

Background: Studies suggest early egg introduction (EEI) in the first year of life is associated with reduced risk of developing egg allergy. No US recommendations exist regarding optimally implementing EEI.

Methods: Using simulation and Markov modelling over a 20-year horizon, we explored optimal EEI strategies applied to US, European and Canadian populations, comparing screening of high-risk infants (skin prick testing [SPT] or serum-specific IgE[slgE]) before introducing cooked egg at 6 months of life vs egg introduction at home, without screening, for all infants.

Results: A no-screen approach dominated egg SPT screening of high-risk infants with early-onset eczema. Base model per-patient incremental costs of SPT were \$6865 US dollars (USD), 6801 euros and \$10 610 Canadian dollars (CAD). For egg slgE screening in primary care settings, base model incremental costs were \$16 722 USD, 18 072 euros and \$28 193 CAD. As the simulation concluded 2.5% were egg allergic without screening vs 9.5%, 12% and 21.4% of children undergoing SPT, delayed introduction or slgE screening. Incremental societal costs from screening reached \$2 009 351 175 USD for SPT and \$4 894 445 790 USD for slgE testing. In sensitivity analyses, if the risk of reaction with initial egg ingestion was $\geq 22.5\%$, SPT before EEI became a preferred strategy. A no-screen approach dominated both EEI of raw pasteurized egg and delayed cooked egg introduction approaches.

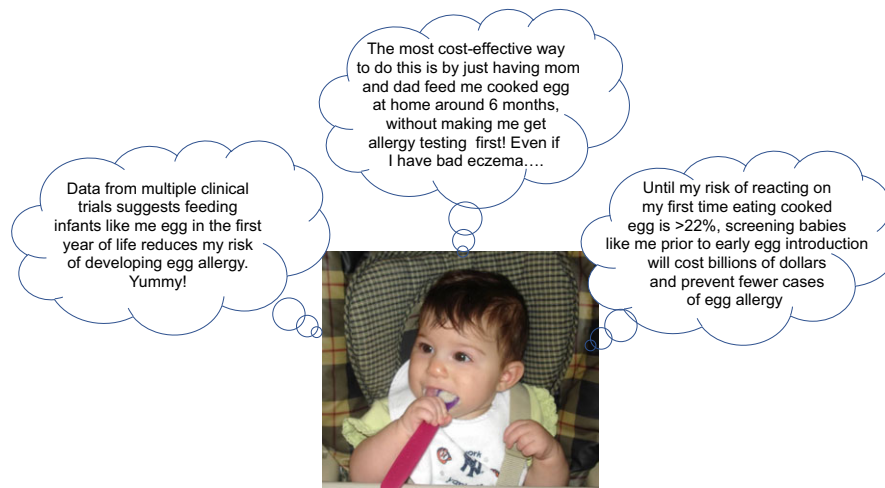
Conclusions: Assuming initial reaction rates $< 22.5\%$, a no-screening EEI cooked egg approach has superior health and economic benefits in terms of number of egg allergy cases prevented and total healthcare costs vs screening testing.

KEYWORDS

cost-effectiveness, egg allergy, oral food challenge, primary prevention, screening

Abbreviations: AAAAI, American Academy of Allergy, Asthma, and Immunology; AAP, American Academy of Pediatrics; AAP, American Academy of Pediatrics; ACAAI, American College of Allergy, Asthma, and Immunology; ARR, absolute risk reduction; ASCIA, Australasian Society for Clinical Immunology and Allergy; BEAT, beating egg allergy; CSACI, Canadian Society of Allergy and Clinical Immunology; CSACI, Canadian Society of Allergy and Clinical Immunology; EAT, enquiring about tolerance; EEI, early egg introduction; EPI, early peanut introduction; HEAP, hen's egg allergy prevention; LEAP, learning early about peanut allergy study; NIAID, National Institute of Allergy and Infectious Diseases; NNT, number needed to treat; PETIT, prevention of egg allergy with tiny amount intake; QALY, quality-adjusted life years; RRR, relative risk reduction; SPT, skin prick testing; STAR, solids timing for allergy reduction; STEP, starting time for egg protection; UK-DOH, United Kingdom Department of Health.

Clinical Trials Registration: Not Applicable.



The Health and Economic Benefits of Early Egg Introduction

GRAPHICAL ABSTRACT

1 | INTRODUCTION

Egg allergy is the 2nd most common childhood food allergy, affecting approximately 0.5%-8.9% of children depending on the country of study and method of assessment.^{1,2} Egg is a unique allergen in that it is somewhat labile and approximately 80% may be tolerant to extensively heated (eg, baked) forms.² Moreover, egg allergy has a favourable natural history compared to other allergens in that upwards of 50% (and even 80% in older literature) may resolve by mid-to-late childhood.¹ Quality of life (QoL) among caregivers of egg allergic children has been shown to be worse, comparatively, to other allergens such as peanut or tree nut, likely due to the ubiquity of egg in the US diet and the difficulty that comes with avoidance.³ Importantly, egg sensitization (and allergy) may be a foreboding risk factor for other food allergy such as peanut, as well as respiratory disease later in childhood.^{1,4-8} Thus, efforts for the primary and secondary prevention of egg allergy are strongly desired.

To date, there have been 6 randomized, placebo-controlled trials (RPCTs) investigating effects between EEI and egg allergy prevention, in both standard-risk and high-risk infants.⁹⁻¹⁴ The Enquiring About Tolerance (EAT) study noted significant absolute risk reductions (ARR) for developing egg allergy only in the per-protocol population favouring EEI between 3 and 6 months of life vs after 6 months of life.¹⁴ The Australian Solids Timing for Allergy Reduction (STAR), Beating Egg Allergy (BEAT) and Starting Time for Egg Protection (STEP) studies noted a trend towards a reduced risk of egg allergy (or sensitization) at 1 year associated with early (<6 months) egg introduction.¹¹⁻¹³ Alternatively, the German Hen's Egg Allergy Prevention (HEAP) study noted no significant differences in rates of oral food challenge (OFC)-proven egg allergy at the age of 1 year.⁹ Lastly, the Japanese Prevention of Egg Allergy with Tiny Amount Intake (PETIT) RPCT of Japanese 4- to 5-month-olds with eczema noted a strongly protective effect (RR 0.22, 95% CI 0.08-

0.61; $P = 0.0012$; NNT 3.4) associated with early consumption of heated egg.¹⁰

Ierodiakonou et al performed a meta-analysis of the body of work surrounding prevention RPCTs, noting "moderate certainty" of evidence that EEI between 4 and 6 months reduced the risk of developing egg allergy (RR 0.56; 95% CI, 0.36- 0.87) based on 5 RPCTs inclusive of 1915 children. However, using trial sequential analysis to determine the extent of additional trial enrollment to provide good certainty of a 30% effect size, they estimated thousands of additional trial participants would be needed.¹⁵

In the past year, both the Australasian Society for Clinical Immunology and Allergy (ASCIA) and the United Kingdom Department of Health (UK-DOH) have published guidelines recommending egg introduction around 6 months of life, without first assessing for egg sensitization, recommending in-office introduction or specifying an amount/frequency for such introduction.^{16,17} However, the United States has no current recommendations for EEI, just for peanut.¹⁸ The American Academy of Allergy, Asthma, and Immunology (AAAAI); American College of Allergy, Asthma, and Immunology (ACAAI); and Canadian Society of Allergy and Clinical Immunology (CSACI) have decided jointly to update their prevention guidelines, and in support of this project, we undertook a cost-effectiveness analysis of the health and economic benefits of EEI strategies to best advise these recommendations.

2 | METHODS

We designed a computer-based mathematical simulation (Tree Age Pro, Williamstown Mass, MA, USA) to evaluate cooked egg introduction strategies for high-risk infants due to early-onset eczema in a US population.¹⁹ Markov modelling was used to reflect recurrent probabilistic risk of inadvertent reactions and development of

tolerance to egg. The majority of studies on EEI have been designed with pasteurized raw egg powder, which contains additional epitopes not found in either cooked or extensively heated egg, which is considered more allergenic and is not customarily part of the US diet.^{1,9,11-13} Our model was based on the PETIT trial data, which evaluated the risks and benefits of early cooked EEI in at-risk infants with eczema (a group highly similar to that in the Learning Early About Peanut Allergy trial).^{4,10,20} The PETIT trial evaluated a two-step EEI strategy, enrolling infants with eczema at 4-5 months of age who were randomized to receive placebo or cooked egg. In the EEI group, the initial daily dose of cooked egg was 50 mg (a potential subthreshold dose to elicit an allergic reaction) and then advanced to 250 mg daily after 3 months. The primary outcome was an open food challenge to 32 g of egg at 12 months of age. Only 8% of in the EEI group developed egg allergy vs 38% in the placebo group, prompting early halting of the trial per prespecified design.¹⁰

In addition to assumptions derived from the PETIT study, models also included age-adjusted all-cause mortality over a simulated 20-year time horizon, with the 2013 US life tables used for base-case and sensitivity analyses.^{21,22} Infant cohorts were assigned to competing strategies of egg introduction: (a) EEI without screening; (b) skin prick test (SPT) screening for egg sensitization through consultation with a board-certified allergist; (c) egg serum-specific IgE (sIgE) testing by primary care provider or (d) delayed egg introduction (>12 months of age) without screening. Rates of positive egg SPT were based on Martin et al²³ who reported a 24% prevalence of positive egg SPT in infants with eczema. Children with positive egg SPT were either assumed to be egg allergic or underwent supervised egg challenge in two distinct arms of the simulation.^{18,24} To evaluate benefit and harm from primary care diagnosis of egg allergy based solely on egg sIgE testing > 0.35 in comparison with other strategies, children with positive sIgE testing received a diagnosis of egg allergy without supervised challenge. Eczema prevalence was modelled from a recent US estimate.²⁵ The natural history of egg allergy resolution was based on Savage et al,²⁶ with the base case assuming an annual tolerance rate of 6.6% in egg allergic infants up to 10 years of age. The annual risk of inadvertent egg allergic reactions was modelled at 5% per annum with the rare outcome of food allergic fatality also included in the simulation.^{27,28} Health state utility of egg allergy was modelled at 0.91 based on data of Carrol and Downs,²⁹ and compounded disutility of allergic reactions upon this health state was excluded in base-case analysis but accounted for in sensitivity analyses.³⁰

Costs of SPT, sIgE testing, initial allergy consultation, incremental grocery costs for egg allergic children and epinephrine autoinjector preparedness costs were included in the base-case model.³¹⁻³⁴ Models also evaluated additional costs of ongoing allergy visits, paediatrician encounters for food allergy, nutritionist visits, alternative provider visits and job-related food allergy opportunity costs. All quality-adjusted life years (QALY) and costs in 2018 dollars were discounted equally at 3% per annum to reflect the average consumer price index for all goods and services.³⁵ Model assumptions and ranges used for deterministic sensitivity analyses are shown in

Table 1. Supplemental analyses were performed on a low-risk general US population with additional simulations in high-risk infants to model optimal strategies in Canadian and European populations using European estimates of direct and indirect costs of food allergy together with costs of specialty paediatric consultation, testing and oral challenges. Canadian costs derived from currency conversion of European costs (Table S1) and further validated by local cost estimates (personal verbal and written communication, Dr. Edmond Chan, MD) with sensitivity analyses performed across ranges including local cost estimates (new patient consultation \$221 CAD, an extended paediatric follow-up visit as substitute for inpatient day challenge \$202 CAD and skin testing cost \$44 CAD). Because Canadian provincial costs may vary, wide sensitivity analyses included oral challenge costs to a lower limit of \$60, skin testing to \$1 and allergist consult fee of \$75.

An additional model was also evaluated optimal strategies for raw pasteurized egg introduction with US economic assumptions (compared to delayed egg introduction). Using data published in the STAR trial, the model incorporated an infancy raw egg reaction rate of 31%, with an egg allergy relative risk of 0.65 (sensitivity 0.25-0.8) for EEI. Data from the BEAT trial were used to estimate the initial reaction rate in SPT-negative infants (8.5%). This study was exempt from IRB review.

3 | RESULTS

In the base-case analysis (Table 2), both testing (either using SPT or sIgE) and delayed introduction strategies were dominated by EEI without testing or in-office introduction where egg was recommended to be universally introduced to all infants, irrespective of risk, at 6 months of life. The per subject incremental cost of egg SPT (followed by confirmatory in-office egg challenge if positive) was \$2179 USD in the base model (\$2234 USD without challenge), but increased to \$6559 USD (\$6865 USD without challenge) when additional provider and job opportunity costs were included. When these additional costs were considered, EEI with skin prick test screening assessment and reflex challenge for egg sensitization cost less than delayed introduction in infants with eczema and resulted in fewer children with egg allergy, but EEI without screening was still the optimal strategy (percentage egg allergic at 20 years: 2.5% early introduction without screening; 9.5% SPT without challenge confirmation; 9.1% SPT with challenge confirmation; 21% sIgE screening; 12% delayed introduction without screening). Interestingly, an approach modelling screening for egg sensitization in the primary care setting using sIgE (followed by avoidance in infants testing positive) was the most costly strategy (incremental per subject cost \$4180 USD base case, \$16 722 USD with additional costs modelled) and as well resulted in the most incremental cases of egg allergy. Over the model horizon, universal EEI without screening was associated with 14.94 QALY, compared with 14.79 QALY for SPT without challenge confirmation, 14.8 QALY for SPT with challenge confirmation, 14.74 QALY for delayed introduction and 14.54 QALY for sIgE screening (suggested minimal clinical important difference for

TABLE 1 Table of probabilities and estimates, with ranges for sensitivity

Variable	Value (range)	Source
US population	327 063 980 persons	19
US census (infants) 2016	4 009 514 infants	22
Prevalence of eczema at 5 mo of age	7.3%	26
US infants with eczema at 5 mo of age	292 695	Derived
Prevalence of low-dose cooked egg reactive in infants with eczema at 6 mo	0% (0-10%)	10
Prevalence of egg sensitization in infants with eczema at 4-5 mo of age (sIgE)	65% (15%-80%)	10
Prevalence of egg sensitization (prick skin testing) in infants with eczema (HealthNuts)	24% (5%-50%)	24
Prevalence of egg sensitization (prick skin testing, raw egg) in infants at 3 mo of age (general population)	3.6% (0.5-5%)	14
Rate of positive challenge with egg prick skin test 3-5 mm or greater in infants with eczema	95% (50%-98%)	25
Egg allergy with early 2-step cooked introduction at 6 mo in infants with eczema	8% (3%-12%)	10.
Egg allergy in infants with eczema without early cooked introduction	38% (10%-45%)	10
Egg allergy in infants with early introduction (general population)	1.4% (0.5%-3%)	14
Egg allergy in infants without early introduction (general population)	5.2% (4%-6%)	14.
Annual rate of egg allergy resolution	6.6% (3.7%-8.5%) up to 10 y of age	23
Annual risk of accidental egg reactions	5% (1%-5)	27
Food allergy fatality risk (paediatric)	3.25 per million person years (3.25-32.5)	28
Cost allergy consultation (initial)	\$673 (\$300-\$900)	34
Cost supervised food challenge	\$121 (\$115-\$250)	34
Cost of egg skin testing	\$24 (\$10-\$40)	34
Cost of egg-specific IgE	\$17 (\$8-\$35)	33
Incremental annual grocery cost of food allergy, base case	\$304 (\$50-\$400)	30
Annual cost of epinephrine twinpack, base case	\$635 (\$0-\$650)	31
Additional costs per annum		
Allergist visits	\$146 (\$0-\$300)	31
Paediatrician visits for food allergy	\$98 (\$0-\$200)	31
Nutritionist visits	\$17 (\$0-\$100)	31
Alternative provider visits for food allergy	\$24 (\$0-\$100)	31, 35
Job-related opportunity costs for food allergy	2544 (\$0-\$5000)	31, 35
Start age	Birth	
Annual discount rate	0.03 (0-0.03)	35
Negative health state utility (QALY) influence for food allergy	-0.09 (-0.01 to -0.1)	29,30
Additional sensitivity analysis on Raw Egg		
Initial reaction rate (no screening, eczema)	31% (10%-40%)	11
Egg allergy relative risk (early introduction, eczema)	65% (25%-80%)	11
Initial reaction rate (skin testing negative)	8.5% (3%-10%)	13

QALY is 0.04-0.08).³⁶ The incremental SPT strategy costs to society (US population) could reach \$2 009 351 175 USD if modelling additional provider and job-related opportunity costs, with sIgE screening strategy incremental costs reaching \$4 894 445 790 USD. When SPT screening was used in the broader population of infants without eczema, the population costs were even higher (Table 3).

In sensitivity analyses, a no-screen strategy in the at-risk infants continued to dominate alternative strategies when first-dose reactions reached 10%, 10-year egg tolerance rates were modelled at 37%, annual accidental egg reactions were 1%, egg allergy fatality

rates were modelled at 10x of base estimates, discount rates were excluded, and the time horizon was set at 75 years (Table 4). When reaction rates to cooked egg upon first introduction exceeded 24.8%, a SPT strategy prior to introduction became the preferred strategy (22.5% if disutility of allergic reactions was included in model). EEI was the optimal strategy in additional sensitivity analyses performed across ranges shown in Tables 1 and S1. Analysis included evaluation of alternative positive predictive values of early egg SPT in the challenge model. Sensitivity of egg SPT modelled at 46% was combined with a 93% specificity²⁴ across varying

TABLE 2 Base-case analysis comparing early egg introduction strategies

Introduction strategy	Cost per subject (base) ^a	Cost per subject (including additional provider and job-related opportunity costs) ^a	QALY per subject	Percentage egg allergic at 20 y (%)	Incremental societal costs (base)						Incremental societal costs (including additional provider and job-related opportunity cost)					
					10% adoption	50% adoption	75% adoption	100% adoption	10% adoption	50% adoption	75% adoption	100% adoption	10% adoption	50% adoption	75% adoption	100% adoption
Infants with eczema																
No screening prior to early introduction	\$557	\$2235	14.94	2.5												
Skin testing, early introduction if negative	\$2791	\$9100	14.79	9.5	\$65 388 063	\$326 940 315	\$490 410 473	\$653 880 630	\$200 935 118	\$1 004 675 588	\$1 507 013 381	\$2 009 351 175	\$200 935 118	\$1 004 675 588	\$1 507 013 381	\$2 009 351 175
Skin testing with office challenge if positive	\$2736	\$8794	14.8	9.1	\$63 778 241	\$318 891 203	\$478 336 804	\$637 782 405	\$191 978 651	\$959 893 253	\$1 439 839 879	\$1 919 786 505	\$191 978 651	\$959 893 253	\$1 439 839 879	\$1 919 786 505
slgE testing, early introduction if negative	\$4737	\$18 957	14.54	21.4	\$122 346 510	\$611 732 550	\$917 598 825	\$1 223 465 100	\$489 444 579	\$2 447 222 895	\$3 670 834 343	\$4 894 445 790	\$489 444 579	\$2 447 222 895	\$3 670 834 343	\$4 894 445 790
Delayed egg introduction	\$2645	\$10 615	14.74	12.0												

^aAll analyses include incremental grocery and autoinjector costs associated with egg allergy.

TABLE 3 Sensitivity analysis of a skin testing early egg introduction strategy in the general population

Introduction strategy	General population	Cost per subject ^a	Cost per subject (including additional provider and job-related opportunity costs) ^b	QALY per subject	Percentage egg allergic at 20 y (%)	Incremental societal costs (base)				Incremental societal costs (including additional provider and job-related opportunity cost)			
						10% adoption	50% adoption	75% adoption	100% adoption	10% adoption	50% adoption	75% adoption	100% adoption
No screening prior to early introduction		\$98	\$391	14.98	0.4								
Skin testing, early introduction if negative		\$1042	\$2080	14.96	1.6	\$378 498 122	\$1 892 490 608	\$2 838 735 912	\$3 784 981 216	\$677 206 915	\$3 386 034 573	\$5 079 051 860	\$6 772 069 146
Delayed egg introduction		\$362	\$1453	14.96	1.6								

All analyses include incremental grocery and autoinjector costs associated with egg allergy.

prevalence estimates of egg allergy from 24% to 38% to generate positive predictive values of 80% to 68%. Even across these ranges (including modelling positive predictive values below 50%), an EEI approach dominated an approach of SPT and subsequent supervised challenge in terms of costs and cases of egg allergy prevented. To explore the effect of very low egg allergy prevalence, analyses in the SPT with reflex challenge arm evaluated point egg allergy prevalence of 1% in at-risk children at the time of challenge. Even at this low prevalence rate, a SPT strategy was dominated by EEI without testing (incremental cost \$831 per patient screened with a net loss of 0.003 QALY per patient at risk).

When evaluating EEI using raw pasteurized egg, the preferred strategy changed and delayed introduction dominated alternative approaches, given the high reaction rate reported in at-risk infants to early introduction of raw egg (Table 5). However, as the relative risk of egg allergy from early introduction of raw pasteurized egg fell below 27%, raw pasteurized EEI dominated delayed introduction. The raw egg model was also sensitive to rates of initial reactions. Below initial raw egg reactivity rates of 17.7% (15.6% if disutility of allergic reactions included), the preferred strategy was introduction of raw pasteurized egg without any screening tests.

In the supplemental Canadian and European analyses, screening models were dominated by cooked EEI (Table S2). No screening prior to cooked EEI costs 2416 euros per subject (\$3769 CAD) compared with 9217 euros (\$14 379 CAD), 9062 euros (\$14 136 CAD), 20 488 euros (\$31 962 CAD) and 11 475 euros (\$17 901 CAD) for screening SPT without challenge, screening SPT with challenge, sIgE screening and delayed cooked egg introduction, respectively.

4 | DISCUSSION

Recent pooled data from well-powered, well-conducted RPCTs of EEI show that there is a statistically significant reduced risk of developing egg allergy associated with EEI.¹⁵ Three countries have updated their infant feeding guidelines, all of which recommend EEI starting at around 6 months of life but without any screening to prevent egg allergy (but do not specify a dose/frequency for this introduction).^{16,17} To date, no such US recommendation exists.¹⁸ Given the desire for the AAAAI, ACAAI, and CSACI to jointly update their food allergy prevention guidelines, we performed this cost-effectiveness analysis to better inform an optimal approach for EEI.

We demonstrate that simulated over a 20-year horizon, a recommendation for EEI in all infants, irrespective of their risk of developing food allergy, at 6 months of life without any screening measures dominated all other strategies considered. This benefit is a result of early egg introduction and prevention of overdiagnosis that results from screening with a cut-off that has <100% specificity for diagnosis, applied at a population level. This universal EEI model was associated with the highest QALY, lowest rates of egg allergy at the end of the model and \$2 billion to \$4.8 billion US dollars in cost-savings when opportunity costs to the caregiver were considered. Multiple

TABLE 4 Selected sensitivity analyses in the US at-risk population (cooked egg)

Introduction strategy	Cost per subject (base)	QALY per subject
Base case		
No screening prior to early introduction	\$557	14.94
Skin testing, early introduction if negative	\$2791	14.79
slgE testing, early introduction if negative	\$4737	14.54
Delayed egg introduction	\$2645	14.74
Prevalence of low-dose cooked egg reactive in infants with eczema at 6 mo, 10%		
No screening prior to early introduction	\$1197	14.88
Skin testing, early introduction if negative	\$2791	14.78
slgE testing, early introduction if negative	\$4961	14.52
Delayed egg introduction	\$2645	14.74
Egg allergy resolution by 10 y of age, 37%		
No screening prior to early introduction	\$807	14.91
Skin testing, early introduction if negative	\$3731	14.7
slgE testing, early introduction if negative	\$6855	14.34
Delayed egg introduction	\$3832	14.62
Annual risk of accidental egg reactions, 10%		
No screening prior to early introduction	\$557	14.94
Skin testing, early introduction if negative	\$2791	14.79
slgE testing, early introduction if negative	\$4737	14.54
Delayed egg introduction	\$2645	14.74
Food allergy fatality risk (paediatric), 32.5 per million person years		
No screening prior to early introduction	\$557	14.94
Skin testing, early introduction if negative	\$2791	14.8
slgE testing, early introduction if negative	\$4736	14.54
Delayed egg introduction	\$2645	14.74
Annual discount rate, 0%		
No screening prior to early introduction,	\$697	19.78
Skin testing, early introduction if negative	\$3317	19.59
slgE testing, early introduction if negative	\$5921	19.28
Delayed egg introduction	\$3309	19.53
Model horizon, 75 y (QALY discount excluded)		
No screening prior to early introduction,	\$3605	70.16
Skin testing, early introduction if negative	\$14 253	69.65
slgE testing, early introduction if negative	\$30 572	68.79
Delayed egg introduction	\$17 125	69.47

sensitivity analyses also confirmed that this approach was robust in the United States. Importantly, while screening approaches were dominated by nonscreening approaches, SPT screening with cooked EEI still dominated delayed introduction, showing the value of EEI. If the risk of an initial cooked egg reaction is >22.5% then SPT before introduction would be a preferred option. Sensitivity analyses demonstrate that pasteurized egg EEI is ill-advised, comparatively, and results in greater rates of egg allergy and reactions upon introduction when compared to cooked EEI.

Universal screening of infants with early-onset eczema, as well as delayed egg introduction, actually increases egg allergy diagnoses with high attendant societal expenditures. Neither strategy is cost-

effective. Therefore, the value of any adoption of a recommendation for EEI involving any screening (similar to recommendations for early peanut introduction) would have to be questioned. In a recent nationally representative US survey of new mothers of infants <1 year and expecting mothers, while EEI around the age of 8 months was supported by 60% of the sample, only 49% and 44% supported use of either SPT or in-office challenge prior to early introduction of any solid food.³⁷ These data were obtained during the roll-out of the NIAID addendum guidelines and represent a cross-sectional glimpse at potential large barriers towards implementing early allergenic solid food introduction at the population level. Opinions on this topic may evolve over time, and

TABLE 5 Sensitivity analysis of introducing cooked egg vs raw, pasteurized egg

Introduction strategy	Cost per subject (base) ^a	Cost per subject (including additional provider and job-related opportunity costs) ^a	QALY per subject	QALY per subject with compounded disability impairment from reactions	Number of allergic reactions per patient at-risk	Cost-effectiveness with opportunity costs (base)	Cost-effectiveness with opportunity costs, compounded disability from allergic reactions	Percentage egg allergic at 20 y (%)
Infants with eczema (cooked egg)								
No screening prior to early introduction	\$557	\$2235	14.94	14.93	0.03	\$150	\$150	2.5
Skin testing, early introduction if negative	\$2791	\$9100	14.79	14.78	0.12	\$615	\$616	9.5
Skin testing with office challenge if positive	\$2736	\$8794	14.8	14.77	0.34	\$594	\$595	9.1
slgE testing, early introduction if negative	\$4737	\$18 957	14.54	14.51	0.26	\$1304	\$1306	21.4
Delayed egg introduction	\$2645	\$10 615	14.74	14.73	0.13	\$720	\$721	12.0
Infants with eczema (raw, pasteurized egg)								
No screening prior to early introduction	\$3345	\$13 421	14.67	14.63	0.49	\$915	\$917	15.2
Skin testing, early introduction if negative	\$4013	\$14 004	14.67	14.65	0.25	\$955	\$956	15.1
Skin testing with office challenge if positive	\$3959	\$13 698	14.68	14.64	0.47	\$933	\$936	14.7
slgE testing, early introduction if negative	\$5713	\$22,872	14.45	14.41	0.42	\$1583	\$1587	25.9

^aAll analyses include incremental grocery and autoinjector costs associated with egg allergy.

additional studies are needed to determine whether screening prior to EEI may be preference-sensitive choice for a caregiver, allergy specialist or primary care provider. Guidelines are recommendations regarding optimal, evidence-based ways to practice, which many may not strictly adhere to, a important consideration for policymakers. However, when making a policy, steps must be taken to ensure that a recommendation has broad support of the key stakeholders, is cost-effective and will produce the anticipated, desired health outcomes.

This study has limitations. This is a simulation, with multiple assumptions based on prior studies. Data inputs were sometimes limited, incomplete or based on trials that have not been replicated. Few EEI trials involved cooked as opposed to raw egg introduction.⁹⁻¹⁴ However, we felt that a cooked egg product was the most natural and preferred form, an assumption further backed by lack of harm and a protective benefit in the per-protocol arm of the EAT study which also used cooked egg for EEI. Simulating the natural history of egg is also difficult given limited published data, but as egg allergy is to a large degree outgrown in childhood, we modelled only a 20-year horizon to account for this (however, sensitivity analyses to 75 years were performed).^{6,26,27} There are limited data regarding rates of food allergy and severe eczema in infants, beyond the existing EEI clinical trials and HealthNuts cohort.^{2,5,9-14,23} It is also unclear what designates someone as “at risk” or “high risk” for egg allergy.¹ This was inconsistent in the egg trials and included nonatopic children with a primary atopic relative, or varying degrees of eczema severity.⁹⁻¹⁴ In this simulation, we used early-onset eczema, similar to the criteria from the PETIT trial, in line with data from large, prospective prevalence studies of food allergy.^{10,18,38} Using multiple trials to derive base estimates may induce heterogeneity and uncertainty, so wide sensitivity analyses were used to account for potential variation in egg allergy prevalence and testing accuracy. We intentionally modelled scenarios in which reflex challenges were performed by board-certified allergists as well as situations where screening testing performed by primary care providers was not followed by allergist consultation because these reflect real-world situations encountered in practice. Furthermore, to characterize downstream unintended consequences of recommendations, we included a low-risk cohort in these analysis to better understand the impact of potential “screening creep” from advice given to high-risk infants. The simulation incorporating reflex challenge in SPT-positive subjects was modelled after sensitivity and specificity data reported by Peters 2013²⁴ and could overestimate cooked egg allergy rates; however, broad sensitivity analyses were performed (50%-90% reactivity rate) to address this limitation. The primary care egg slgE model was deliberately modelled to evaluate benefits and harms of isolated slgE screening for diagnosis. Referral of such children with positive egg slgE testing for challenge may result in different outcomes; however, such outcomes would neither be less costly nor more effective than the simulation arm modelling screening SPT and reflex challenge. Health state utility of egg allergy was modelled at 0.91 based on data of Carrol and Downs,²⁹ who derived values reported by parents of nonfood allergic children. Similar estimates

from caregivers of food allergic children are not available, and it is possible that further health state utility assessment in different populations may result in different reported values. While a minimally clinically important difference (MCID) for QALY between 0.04 and 0.08 has been proposed, this has not been studied in food allergy and it is unclear whether this MCID is applicable per se given MCID is index and disease-specific.³⁶ In modelling over a many-year horizon, the cumulative MCID becomes reflective of the aggregate of diagnoses and allergic episodes, and because screening may delay opportunities for early introduction, any benefit in preventing an index food allergic episode becomes overshadowed by additional allergic reactions that may have been prevented through early induction of tolerance. In this analysis, screening strategies are dominated by EEI in terms of both cost and QALY. There are also no real-time data to understand EEI as a healthcare policy. We modelled a conservative approach similar to recommendations for peanut in the NIAID addendum guidelines in assessing for preexisting egg sensitization either with egg sIgE or SPT in at-risk patients, although no such approach has been recommended in any country.¹⁸ However, it is reasonable to presume that any future US guideline might strongly consider this approach.

Our cost inputs are highly specific to US, Canadian and European children and may not necessarily generalize elsewhere. Population data used in the simulations were derived from select studies with potential generalizability limitations on a broader scale. It is important to note that the PETIT study (which was stopped early due to its success, by design) was a central modelling input, and while it is unique in its approach to cooked EEI, the initial amounts introduced were quite low, possibly representing “silent” immunotherapy in some children, and it is possible EEI of larger amounts could lead to different effects. Further studies are needed to reproduce the PETIT results and test introducing larger initial amounts. Lastly, we did not directly model the impact attributable to wait times to see an allergy specialist with the screening approach, or the consequences of unintended delayed introduction beyond age of 12 months that could result from such access to care issues. However, despite these limitations, the model was robust to multiple sensitivity analyses and denotes a rate of reactivity above which a screening approach would be cost-effective.

There is strong evidence supporting EEI can decrease the risk of developing egg allergy. While the United States has no existing policy for this, the UK, Australia and New Zealand recommend EEI around 6 months of life, without any preassessment and irrespective of the infant's risk for developing food allergy.^{16,17} In recommending any medical screening test, it should have a positive impact on the natural disease history in those with a positive test. This analysis demonstrates that screening for egg allergy would do the opposite, leading to greater allergy risk and cost. In support of consideration of a recommendation for EEI for forthcoming joint food allergy prevention guidelines from the AAAAI, ACAAI, and CSACI, this simulation shows that a recommendation for EEI of cooked egg at 6 months of life in all infants irrespective of risk produces the most optimal health and economic benefits compared to alternative strategies involving

screening. A screening approach for EEI is associated with costs >\$1 billion US and prevents fewer cases of egg allergy compared to not screening. Thus, we recommend that policymakers tasked with determining how to implement EEI should strongly consider adopting a similar strategy to that taken by the UK-DOH and ASCIA.^{16,17}

CONFLICTS OF INTEREST

Marcus Shaker has a family member who is CEO of Altrix Medical.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table e1: Table of Probabilities and Estimates with International Sensitivity Inputs

<u>Variable</u>	<u>Value (range)</u>	<u>Source</u>	<u>European (range)</u>	<u>Canadian (range)</u>	<u>E-source</u>
US population	327,063,980 persons	19	--	--	
US census (infants) 2016	4,009,514 infants	22	--	--	
Prevalence of eczema at 5 months of age	7.3%	26	14.2%	8.5%	e1, e2
US infants with eczema at 5 months of age	292,695	Derived	--	--	
Prevalence of low-dose cooked egg reactive in infants with eczema at 6 months	0% (0-10%)	10	0% (0-10%)	0% (0-10%)	
Prevalence of egg sensitization in infants with eczema at 4-5 months of age (sIgE)	65% (15%-80%)	10	65% (15%-80%)	65% (15%-80%)	
Prevalence of egg sensitization (prick skin testing) in infants with eczema (HealthNuts)	24% (5% - 50%)	24	24% (5% - 50%)	24% (5% - 50%)	
Prevalence of egg sensitization (prick skin testing, raw egg) in infants at 3 months of age (general population)	3.6% (0.5-5%)	14	3.6% (0.5-5%)	3.6% (0.5-5%)	
Rate of positive challenge with egg prick skin test 3-5mm or greater in infants with eczema	95% (50% - 98%)	25	95% (50% - 98%)	95% (50% - 98%)	
Egg allergy with early 2-step cooked introduction at 6 months in infants with eczema	8% (3% - 12%)	10.	8% (3% - 12%)	8% (3% - 12%)	
Egg allergy in infants with eczema without early cooked introduction	38% (10% - 45%)	10	38% (10% - 45%)	38% (10% - 45%)	
Egg allergy in infants with early introduction (general population)	1.4% (0.5% - 3%)	14	1.4% (0.5% - 3%)	1.4% (0.5% - 3%)	
Egg allergy in infants without early introduction (general population)	5.2% (4% - 6%)	14	5.2% (4% - 6%)	5.2% (4% - 6%)	
Annual rate of egg allergy resolution	6.6% (3.7% - 8.5%) up to 10 years of age	23	6.6% (3.7% - 8.5%) to 10 years of age	6.6% (3.7% - 8.5%) to 10 years of age	
Annual risk of accidental egg reactions	5% (1%-10%)	27	5.5% (1%-10)	5% (1%-10)	
Food allergy fatality risk (pediatric)	3.25 per million person years (3.25 – 32.5)	28	3.25 per million person years (3.25 – 32.5)	3.25 per million person years (3.25 – 3.25)	
Cost allergy consultation (initial)	\$673 (\$300-\$900)	34	102 euro (75-300)	159 (75-300)	e3, e6
Cost supervised food challenge	\$121 (\$115 - \$250)	34	867 euro (450 – 1,400)	1,353 cad (60 – 1,400)	e4, e5, e6
Cost of egg skin testing	\$24 (\$10-\$40)	34	32 euro (20 – 60)	50 cad (1 – 60)	e4, e5, e6
Cost of egg specific IgE	\$17 (\$8 - \$35)	33	15 euro (10-30)	23 cad (10-60)	e4, e5, e6
Incremental annual grocery cost of food allergy, base case	\$304 (\$50 - \$400)	30	direct costs	direct costs	
Annual cost of epinephrine twinpack, base case	\$635 (\$0 - \$650)	31	direct costs	direct costs	
<u>Additional Costs per annum</u>					

<i>Allergist visits</i>	\$146 (\$0 - \$300)	31	direct costs	direct costs	
<i>Pediatrician visits for food allergy</i>	\$98 (\$0 - \$200)	31	direct costs	direct costs	
<i>Nutritionist visits</i>	\$17 (\$0 - \$100)	31	direct costs	direct costs	
<i>Alternative provider visits for food allergy</i>	\$24 (\$0 - \$100)	31, 35	direct costs	direct costs	
<i>Job related opportunity costs for food allergy</i>	2544 (\$0 - \$5,000)	31, 35	direct costs	direct costs	
Annual direct costs (travel costs, hospital admissions, cost of medication, help with domestic duties, cost of leisure and food, lost earnings)			1,211 euro (800 – 3,000)	1,889 cad (800-3,000)	e5, e6, e7, e8
Annual indirect costs (lost productivity, restricted activity days, reduction in human capital, time spent on information seeking, lost leisure time)			2,862 euro (1,500 – 5,000)	4,465 cad (1,500 – 5,000)	e5, e6, e7, e8
Start age	Birth		Birth		
Annual discount rate	0.03 (0 - 0.03)	35	0.03 (0-0.3)		
Negative health state utility (quality of life) influence for food allergy	-0.09 (-0.01 - -0.1)	29,30	-0.09 (-0.01-0.1)		

Supplemental eTable 1 references

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Table e2: Comparative Cost-Per-Subject of Early Egg Introduction Strategies by Country

Introduction Strategy	Cost per subject (including additional provider and job-related opportunity costs)*			QALY Per Subject	Percent Egg Allergic at 20 years
	US Dollars	Euros	Canadian Dollars		
<u>Infants with Eczema</u>					
No screening prior to early introduction	\$2,235	€ 2,416	\$3,769	14.94	2.5%
Skin testing, early introduction if negative	\$9,100	€ 9,217	\$14,379	14.79	9.5%
Skin testing with office challenge if positive	\$8,972	€ 9,062	\$14,136	14.8	9.1%
slgE testing, early introduction if negative	\$18,957	€ 20,488	\$31,962	14.54	21.4%
Delayed egg introduction	\$10,615	€ 11,475	\$17,901	14.74	12.0%
*all analyses include incremental grocery and autoinjector costs associated with egg allergy					